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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61F 2/06 | A1

(11) International Publication Number: **WO 00/47136**

(43) International Publication Date: 17 August 2000 (17.08.00)

(21) International Application Number: PCT/US00/03603

(22) International Filing Date: 14 February 2000 (14.02.00)

(30) Priority Data:
60/119,995 12 February 1999 (12.02.99) US

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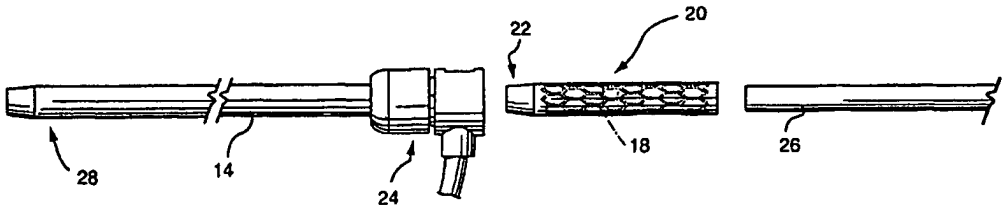
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: VENOUS VALVE IMPLANT BIOPROSTHESIS AND ENDOVASCULAR TREATMENT FOR VENOUS INSUFFICIENCY



(57) Abstract

A vascular valve prosthesis is formed by suturing, preferably in a running fashion, a vein valve segment that has been substantially trimmed to reduce a wall thickness, and thus a radial dimension thereof, to a self-expanding stent. The thus formed bio-prosthesis (18) is percutaneoulsy placed to treat chronic venous insufficiency when it is due to incompetent venous leaflets.

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VENOUS VALVE IMPLANT BIOPROSTHESIS AND ENDOVASCULAR TREATMENT FOR VENOUS INSUFFICIENCY

This application claims the benefit of U.S. Provisional Application Serial No. 60/119,995, which was filed February 12, 1999, the disclosure of which is incorporated herein by this reference.

DESCRIPTION OF THE RELATED ART

Two percent of the United States population suffers from severe forms of venous insufficiency. It is a significant health problem since the condition affects a wide range of ages, from pre-teenagers to the elderly. Symptoms include dilated veins, leg pain, swelling, and stasis skin changes such as discoloration, lipodermatosclerosis, ulcerations, and recurrent deep venous thrombosis (DVT). The disease carries a significant morbidity that includes frequent hospitalizations and absence from work, recurrent debilitating symptoms despite treatment and changes in lifestyle.

The underlying pathophysiologic mechanism in chronic venous insufficiency is venous hypertension, particularly during the systolic phase of the cardiac cycle. The venous hypertension may be due to outflow obstruction, reflux or a mixed problem. Reflux, frequently the sequelae of venous thrombosis, produces distal venous hypertension equal to the hydraulic pressure resulting from a vertical column of blood (extending from the heart to the ankle) in the upright position. Venous reflux is the result of valvular dysfunction due to prior trauma (valves become scarred or destroyed after thrombus), congenital absence, or incompetence. After an episode of deep vein thrombosis (DVT), patients may present years or even decades later with post-thrombotic syndrome. The initiating event may have been prior surgery, trauma, fractures, pregnancy, and/or prolonged standing or immobility.

The diagnostic evaluation of these patients may include hypercoagulability testing, color duplex ultrasound, and ascending and descending (i.e., contrast) venography.

Medical and surgical treatments are used to treat this condition with moderate success. Medical management aims to control symptoms whereas surgical treatments attempt to restore normal physiologic mechanism. The choice of surgical or non-surgical treatment is based on the severity of symptoms and the anatomic system(s) affected by the disease process. Medical treatments include external compression (compression wraps, elastic compression stockings, and intermittent pneumatic compression devices) and pharmacologic agents. External compression blocks the transcapillary fluid flow during ambulatory venous pressure cycle and causes an increase in the fibrinolytic activity of the veins. Surgical treatments include ligation and stripping of the superficial system, subfascial ligation of incompetent perforating veins, venous reconstructive surgery, crossover saphenofemoral venous bypass, saphenous bypass in patients with isolated obstruction; venous valvuloplasty, venous segment transfer, and vein valve transplantation.

Recently, some investigators described the use of endoscopic venous valve transplantation and restoration of vein competence with a xenograft monocusp valve. See, e.g., Garcia-Rinaldi R, et al., "Femoral vein valve incompetence: treatment with a xenograft monocusp patch," *J Vasc Surg*, 1986,3:932-935 and Ofenloch JC, et al., "Endoscopic venous valve transplantation with a valve-stent device," *Ann Vasc Surg*, 1997;11:62-67. Others have reported a technique of autogenous valve reconstruction at the saphenofemoral junction by creating a proximal saphenous stump, and invaginating it to create a bicuspid valve (Plagnol P, et al., "Autogenous valve reconstruction technique for post-thrombotic reflux," *Ann Vasc Surg*, 1999;13:339-342), or creating the valve by vein

wall intussusception (Wilson NM, et al., "In situ venous valve construction," *Br J Surg*, 1991;78:595-600). Cardon JM, et al. have described the use of ipsilateral saphenous vein as a valve transplant. See "Use of ipsilateral greater saphenous vein as a valved transplant in management of post-thrombotic deep venous insufficiency: long term results," *Ann Vasc Surg*, 1999;13:284-289. To date, the latter produces the most encouraging results, but it is limited by eventual degeneration of the transplanted valves, or inadequate donor valves. In "Experimental prosthetic vein valve," *Int Angiol* 1989;8:7-9, Taheri, et al. have described the use of an experimental prosthetic vein valve in a dog model as an alternative to autogenous venous transplantation.

Despite these therapeutic options, the results have been mixed. Medical treatment may be efficacious and cost effective, but demands strict adherence to a program of ambulatory venous compression. Surgical treatment requires skillful, meticulous technique. Often patients may require multiple interventions. Moreover, the use of compression stockings is often required even after surgical intervention to ensure relief of symptoms and durability of the operation. Some consider the need for compression garments as a proof that surgery was unsuccessful. Thus, it is evident that a need remains for the development of more effective products and procedures for the treatment of chronic venous insufficiency.

BACKGROUND AND SUMMARY OF THE INVENTION

Percutaneous techniques have emerged as less invasive options in the treatment of vascular problems.

Martin, LW, et al. evaluated the feasibility of percutaneous deployment of a venous stent valve in the bovine central venous system, as reported at the SCVIR 22nd Annual Scientific Meeting, March 8-13,

1997, Washington, D.C. Martin et al. obtained two gluteraldehyde-fixed bovine jugular veins with a single valvular apparatus from Baxter Healthcare Corp. One vein valve segment measured 13.9 mm in diameter. He trimmed this vein of excess tissue (no details given) and sutured it inside a self-expanding Nitinol stent (15mm X 28mm). The second vein valve segment measured 8.9 mm in diameter. He trimmed it of excess tissue (no details given) and sutured it to a Gianturco-Rosch Z stent (Cook, Inc., Bloomington, IN). In his single experiment, he percutaneously placed the first bioprosthesis; reportedly confirmed newly established in vivo venous valve competence, inferior vena cava patency and valve leaflet function; and then immediately sacrificed the animal. The second prosthesis was saved for future use.

Martin et al. supplied to us and we used in our first experiment the vein segment from his second prosthesis. We sutured that vein segment to a self-expanding Nitinol stent using spot sutures as was done by Martin et al. We prepared the remaining bioprostheses used in our study, using different trimming techniques than those apparently used by Martin (according to the bioprosthesis he supplied). Also, as detailed hereinbelow, for our third and subsequent experiments we used a different suturing technique and for all our experiments we used a different delivery technique, than was utilized by Martin et al.

It was an object of the invention to develop a bioprosthesis for use in providing or restoring valvular function in a biological duct of a patient. More particularly, it was an object of the invention to provide a system for potential use in treatment of chronic venous insufficiency by using percutaneous techniques. The foregoing and other objects of the invention have been realized by percutaneously placing an endovascular device comprising a vein valve segment that has been substantially trimmed to reduce a radial dimension thereof and sutured, preferably in a

running fashion, to a self-expanding stent, to treat chronic venous insufficiency when it is due to incompetent venous leaflets.

More specifically, using the concept of endoluminal stent graft, a bovine jugular vein with a valve was sutured to a Nitinol stent and deployed in the swine venous system. As noted above, for our first experiment, we used the second bioprosthesis prepared by Martin et al. To prepare the bioprostheses for our remaining experiments, segments of glutaraldehyde-fixed bovine external jugular vein with valves were substantially trimmed, as detailed hereinbelow, and sutured, as also detailed herein, below to a self-expanding, Nitinol stent.

In our first series of experiments, each of eleven animals were premedicated and anesthetized (n=11). Venography of the right external jugular vein, inferior vena cava (IVC), and common iliac vein was performed. Deployment was accomplished via a sheath (12F-24F) using fluoroscopic guidance. Eleven (11) bioprostheses were deployed in the eleven (11) animals. Bioprostheses were deployed in the IVC (n=3) or right external iliac vein (n=6). Animals were sacrificed immediately after deployment (n=7), at one week (n=1), or at two (n=2) weeks. One animal was found dead in the cage. At necropsy, each bioprosthesis (n=4) was explanted, and histopathologic analysis performed. We used the right external jugular vein as the entry site for percutaneous implant delivery. It is potentially possible to place the device in the same manner in human patients. However, since it is possible to construct small bioprostheses with the techniques we have developed, as described herein above, it would be possible to use alternative routes of delivery such as the popliteal vein (posterior aspect of the knee) without the need to predilate the vein, which can disadvantageously activate a myriad of thrombogenic reactions in response to the balloon injury.

The deployments of the bioprostheses were successful in 9 of 11 swine. Two deployments were unsuccessful (one accidental deployment in the right renal vein, one deployment in the IVC caused rupture of the vein). Post-deployment venography (n=9) confirmed no reflux (in the recumbent position of the swine) of the valve leaflets and patency of the vein inferior to the level of the bioprostheses. In the first group of animals (n=5), valve leaflets were normal and competent. In the survival animal group (n=4), the bioprostheses remained patent without evidence of thrombus formation by ascending and descending venography. Gross inspection of the explanted bioprostheses (n=4) demonstrated grossly normal valves that fully occluded the lumen. Complications included hemarthrosis (n=1), death (n=1), and, in our first experiment, bioprosthesis thrombosis immediately after deployment (n=1). Histopathologic analysis showed endothelial cells covering the luminal surfaces. The wall of the bioprostheses had granulomatous response and foreign body reaction. Bacterial contamination was noted in one bioprosthesis.

Our studies show that deployment of a glutaraldehyde-fixed bovine vein sutured to a self-expanding Nitinol stent in the swine iliac vein or IVC is technically feasible and, in the cases where the vein segment is substantially trimmed, will remain patent following deployment. A venous bioprosthesis that can be placed percutaneously may have important clinical applications as an endovascular treatment for chronic venous insufficiency when it is due to valvular incompetence.

BRIEF DESCRIPTION OF THE DRAWINGS

These, as well as other objects and advantages of this invention, will be more completely understood and appreciated by careful study of the following more detailed description of the presently preferred

exemplary embodiments of the invention taken in conjunction with the accompanying drawings, in which:

FIGURE 1 is a digital image of a segment of a glutaraldehyde-fixed bovine jugular vein with leaflets;

FIGURE 2 is a digital image of, in the order recited from the top of the image, a bovine vein segment before trimming, a vein segment axially and radially trimmed and sutured to a Nitinol stent thereby to define a bioprosthesis embodying the invention, and a compressed and loaded bioprosthesis within an introducer according to the present invention;

FIGURE 3 is a schematic illustration of an introducer sheath with dilator;

FIGURE 4 is an schematic, exploded elevational view illustrating the loading of the introducer sheath in an embodiment of the invention;

FIGURE 5 is a schematic elevational view illustrating the deployment of the bioprosthesis in an embodiment of the invention;

FIGURE 6 is a digital image showing a pre-deployment baseline flow through the vein (venogram; injection rate 15cc/sec, total volume 30cc);

FIGURE 7 is a digital image showing the unsheathing of the bioprosthesis at the level of the right iliac vein;

FIGURE 8 is a digital image after bioprosthesis deployment, with the stent fully expanded;

FIGURE 9 is a digital image showing flow through the vein (descending venography) two weeks after bioprosthesis deployment,

showing the column of contrast is interrupted at the level of the competent leaflets;

FIGURE 10 is a digital image showing flow through the vein (ascending venography) two weeks after bioprosthesis deployment, showing a continuous column of contrast and no thrombus formation superior or inferior to the bioprosthesis;

FIGURE 11 is a digital image of bovine vein segment after fixation and containing valve leaflets longitudinally bisected to show the leaflets are normal in appearance, i.e., membranous, pleated and free of thrombus;

FIGURE 12 is a digital image of a microscopic view of a valve segment (longitudinal view, 13X magnification, Masson's Trichome stain) composed of densely collagenous connective tissue with thin bands of smooth muscle, showing reactive endothelial cells are more prominent at the base (arrowheads) and commissure of the valve;

FIGURE 13 is a digital image showing foreign body reaction in the outer two-thirds of the bovine graft (arrows); there is marked remodeling of the normal stromal and cellular architecture. Dense nodular aggregates of macrophages are seen in the ab-lumenal aspect of the vein wall (small circle), as well as a large number of foreign body type multinucleated giant cells (large circle).

DETAILED DESCRIPTION OF THE INVENTION

Segments of a glutaraldehyde-fixed bovine jugular veins (n=11) with leaflets were used. One glutaraldehyde-fixed bovine jugular vein was supplied by Martin, as noted above, and without further trimming by us was sutured with isolated sutures to a Nitinol mesh stent. The remaining glutaraldehyde-fixed bovine jugular veins were obtained by us

from Venpro, Irvine, CA. (FIGURE 1). Bovine vein diameter ranged from 8.9 mm to 14 mm. Each segment obtained from Venpro was substantially trimmed by us to remove at least about 50% of the excess tissue around each vein. More specifically, we trimmed the vein segment to an axial length corresponding to or, more preferably, less than the length of the stent, and we dissected the excess tissue so that the wall thickness of the vein was reduced to at least about 50% of its original thickness. By way of example, we removed approximately 1-3 mm of the initial wall thickness of the veins. We recognized, and our experiments have confirmed, as detailed hereinbelow, that the trimming process is important from a mechanical standpoint because a smaller, more compressible design can be delivered via a smaller system, more suitable for percutaneous techniques. Moreover, when histopathologic analysis is performed, the advantage of having a thinner piece of foreign tissue is that the "host" has to process this tissue and eventually convert it into its own cellular elements. If the host is exposed to less tissue to process, i.e. a substantially trimmed vein segment according to our invention, this can be done in less time, increasing the chances of patency and decreasing the possibility of thrombosis. Substantial trimming according to our invention also helps to keep the functional lumen of the bioprosthesis in close correspondence to the vein in which the bioprosthesis is implanted. Moreover we have found that the substantially trimmed vein segment can be more easily secured with respect to the stent so as to closely appose the stent structure, so that the secured vein segment and stent act as a one piece assembly. This helps in the process of expansion of the bioprosthesis, obtaining a better apposition of the bioprosthesis against the host vein and the achievement and maintenance of a patent passage therethrough.

Self-expanding Nitinol stents (Symphony, Meditech, Boston Scientific, Watertown, MA) were selected to match the diameter of each

of the vein segments. For our second and subsequent experiments, the vein segment with leaflets, radially and axially trimmed as noted above, was placed inside the Nitinol stent. As illustrated in FIGURE 2, the vein segment is preferably trimmed to an axial length less than that of the stent. Providing a vein segment having a length less than that of the stent defines a staged or stepped transition between the edge of the vein segment, the stent, and the host vein. A staged transition is helpful to anchor the device better and also to provide a smoother transition between the device and the host vein, therefore minimizing turbulent flow in these areas thereby reducing the potential for thrombosis formation.

For our second experiment, the trimmed vein was sutured to the stent using discrete sutures. Following implantation we observed that while the prosthesis appeared patent, it appeared to have an irregular diameter, suggesting that the vein segment was sagging between sutures. Accordingly, for our third and subsequent experiments, the trimmed vein was sutured to the stent using 6-0 Prolene (Ethicon, Inc., Johnson & Johnson, Sommerville, NJ) in a running fashion. More specifically, rather than placing isolated sutures in select locations as was done by Martin et al. and for our first and second experiments, we sutured the vein with at least one continuous suture along substantially the entire stent, so that the vein is substantially completely apposed to the stent. This assured that the vein segment would not collapse inside the stent in the process of being delivered or following deployment. Moreover, with the above described trimming and suturing technique, we have found that neither stabilizing sutures nor mechanical dilation is required since the device can substantially fully open and appose to the host vein wall.

After constructing the bioprostheses, the competency of the valve leaflets of each was tested by manually infusing normal saline with a

10cc syringe in the direction opposite to the blood flow. Each bioprosthesis was kept in a glutaraldehyde bath until the time of implant.

Eleven 25-35Kg female swine were used. The Animal Care and Use Committee at our institution approved this research protocol. The day of experiment, each animal was premedicated with Acepromazine Maleate 1.1mg/Kg IM, Ketamine Hydrochloride 22 mg/Kg IM, and Atropine Sulfate 0.8 mg/Kg IM. Thiopental 15 mg/Kg IV was used for induction. Isoflurane 1.5%-2-5% was used for maintenance anesthesia. The right external jugular vein was dissected and used as venous access. An 8.5F vascular sheath (C.R. Bard, Inc., Billerica, MA) was advanced into the jugular vein. Venography of the right iliac vein and IVC was performed using a 5F marker pigtail catheter (Cook Inc., Bloomington, IN) to correct for magnification. Contrast was injected at a rate of 15 cc per sec for a total of 30 cc (FIGURE 6). Each animal was heparinized with 300-400 units/Kg administered intravenously. Prior to implantation, each bioprosthesis was submerged in an ice bath to facilitate crimping and placement inside the introducer/deployment system. We loaded the cooled, reduced diameter bioprosthesis into an introducer tube (FIGURE 2) to facilitate loading into the deployment system, as described in greater detail herein below. The transverse diameters of the right external iliac vein and inferior vena cava (IVC) at specific locations were measured using an electronic caliper. Measurements were obtained in the AP position. The selection of the site for deployment was made to match the diameter of the swine's vein (IVC or iliac vein) to the transverse diameter of the bioprosthesis. Prior to bioprosthesis deployment, the vascular sheath and catheter were removed over an Amplatz superstiff wire (Meditech, Boston Scientific, Watertown, MA). With reference to FIGURE 3, a long deployment system 10 (Cook, Bloomington, IN) ranging from 12F to 24F (12F (n=1), 16F (n=6), 18F (n=3), 24F (n=1)) was advanced into the venous system,

using the right external jugular vein as the entry site, over the guidewire 12. The deployment sheath size was selected based on in vitro experience. We developed the "n+4 French" rule. The rule states that "n" are the diameter of the bioprosthesis, and the deployment sheath should be at least "n+4" French (F). We only used one 24F delivery system (in the first experiment) since it was the only diameter that would accommodate the bioprosthesis formed from the vein segment obtained from Martin et al. For the remaining experiments we were able to use smaller delivery systems due to our trimming and suturing techniques.

With reference to the schematic illustrations of FIGURES 3-5, the selected deployment sheath 14 with inner dilator 16 were advanced over the wire 12. The inner dilator 16 and wire 12 were then removed. As mentioned above, the bioprosthesis 18 (not shown in FIGURE 4) was cooled to reduce its diameter and preloaded in an introducer tube 20. The introducer 20 has an inner diameter equal to or less than the inner diameter of the deployment sheath 14 so that the bioprosthesis can be readily loaded from the introducer to the sheath. We created an introducer by cutting off the distal portion of the deployment sheath of another deployment system of the same size as the selected deployment system 10. However, the introducer could be created as an independent component.

To load the bioprosthesis, the tapered tip 22 of the introducer 20 was pushed into the one-way valve 24 of the deployment system 10; and the bioprosthesis was pushed into the deployment sheath 14 with the aid of a pusher 26. The pusher has an outer diameter that can be accommodated in the inner bore of the introducer and in the inner bore of the sheath 14 and a length greater than that of the sheath so that the pusher can displace the bioprosthesis from the introducer into the sheath and along the sheath to the target portion of the vessel for deployment.

We created a pusher by cutting off the tapered end of the inner dilator 16 of the deployment system 10.

The deployment was accomplished by unsheathing the bioprosthesis (FIGURES 5, 7,8). More specifically, once the bioprosthesis 18 was displaced by the pusher 26 to the distal end 28 of the deployment sheath 14, the deployment sheath 14 was displaced proximally, as shown by the arrow in FIGURE 5, relative to the bioprosthesis 18 and pusher 26, so that the bioprosthesis 18 is disposed in the vessel and is free to self-expand, due to the ambient temperature and its memory characteristics, to substantially fully open and appose the host vein wall (FIGURE 8).

In our experiments, as detailed herein above, we used self-expanding stents so that mechanically expansion such as with a balloon catheter, which may damage the valve and/or vein segment, was not required. As also noted above, the self-expanding stents we selected were Nitinol stents manufactured by a particular manufacturer. However, as will be appreciated by those skilled in the art, self-expanding stents formed from other material(s), having other structural configurations, and/or produced by other manufactures could be used to advantage in accordance with the invention. Thus, the invention is not to be limited to the particular stent used in our experiments.

In our experiments, as described above, the delivery procedure did not require and did not use an over the wire system to deploy the bioprosthesis. The wire was used solely to place the deployment sheath. This was advantageous in that it minimized the possibility of damage to the delicate leaflets of the bioprosthesis or of potentially dislodging the vein from the stent. Furthermore, as noted above, we did not have to dilate any of the bioprostheses we prepared after delivery. The need to dilate afterwards could be potentially damaging to the device. We found

that with our trimming and suturing techniques, neither stabilizing sutures nor post deployment dilation were required since they could fully open and appose the host vein wall.

Post-deployment ascending and descending venography were performed in the recumbent position. Venography was performed to evaluate patency, thrombosis and valvular competency. Descending venography was performed via right external jugular vein access. Ascending venography was performed at the time of sacrifice by exposing the right femoral vein by cutdown and placing a 6F vascular sheath.

Seven animals were sacrificed immediately after implantation of the bioprosthesis with an overdose of Thiopental IV and 30 cc of supersaturated solution of Potassium Chloride (KCl). Gross examination included evaluation of the valvular apparatus by infusing normal saline with a 10 cc syringe as it was done before implantation.

Four animals were selected for the survival group (four animals for two weeks). Anticoagulation consisted of Warfarin Sodium, 2.5 mg orally prior to the procedure and daily thereafter. Ten thousand units of Heparin IV and 44,000 units/Kg of Penicillin G benzathine/Penicillin G procaine were administered during the procedure. Each bioprosthesis was deployed in the same fashion as previously described. Descending venography was performed immediately after deployment. The right external jugular vein was ligated and the incision was closed with 2-0 Vycril (Ethicon, Johnson & Johnson, Somerville, NJ). Each animal received 60 mg SQ of Enoxaparin Sodium immediately afterwards.

Two of the four (4) animals that survived for two (2) weeks were evaluated after bioprosthesis deployment with ascending and descending venography (FIGURES 9,10). Explanted bioprostheses

(n=4) were submitted for light microscopic analysis. Each bioprosthesis was longitudinally bisected between the leaflets. One segment was infiltrated with, and imbedded in hard plastic. The surface was stained with Hematoxylin and Eosin (HE) and saffron stains. In the other segment, the metallic components of the stent were carefully removed, step-cut longitudinally, and the step sections imbedded in paraffin. Serial sections were prepared and stained with HE, Masson's Trichome (MT) and Verhoeff's Van Gieson (VVG) stains.

Nine of the eleven bioprostheses were percutaneously deployed. Six were deployed in the external iliac vein and three in the IVC. Two inadvertent malpositions occurred, one in the right renal vein and one in the peritoneal cavity. These malpositions occurred when attempting to advance the delivery system into a better position for deployment after the wire was removed.

In the acute animal group (n=7), four descending venograms were performed demonstrating competent leaflets, with interruption of the column of contrast at the level of the leaflets. One bioprosthesis (the one made using the vein segment supplied by Martin) was occluded by thrombus. One was inadvertently placed in the right renal vein. One bioprosthesis was found in the peritoneal cavity after inadvertent rupture of the intrahepatic IVC during advancement of the deployment system. The descending venogram showed contrast extravasation indicating IVC rupture. Four ascending venograms were performed in the acute group. These demonstrated fully retracted valve leaflets, without obstructing the flow of contrast. The ascending venograms were omitted in the two inadvertent malpositions and in the occluded bioprosthesis immediately after deployment.

In the survival group (n=4), four descending venograms were performed at the time of implantation of the bioprostheses. In all cases,

the leaflets appeared competent, the bioprostheses fully expanded and free of thrombus. Of the four survival animals, all on warfarin therapy, one animal had to be sacrificed prematurely at one week due to spontaneous hemarthrosis as noted by limping, swelling and discoloration of the hind legs. One animal was found dead in the cage at one (1) week, presumably from exsanguination due to the extensive amount of blood found in the cage. Ascending and descending venography was performed in three (3) of the four (4) animals. In all descending venograms performed (n=3), the leaflets were competent, with interruption of the column of contrast at the level of the competent leaflets. A continuous column of contrast was seen in all ascending venograms performed (n=3), indicating that the valve leaflets were fully retracted (FIGURES 9,10), and that there was no thrombus formation. No migration of the bioprostheses was documented in the acute or the survival groups.

At necropsy, gross inspection at the time demonstrated competent leaflets, fully expanded bioprostheses, and three (3) devices free of thrombus. A single bioprosthesis had post-mortem thrombus entrapping the valve leaflets, which appeared otherwise grossly normal. Light microscopic examinations of the leaflets showed normal tissue, i.e., membranous and variably pleated valves (FIGURE 11).

Endothelial cells were particularly prominent in the valve recesses and commissures (FIGURE 12). However, microscopic examination showed histologically normal valve leaflets (n=4). In the outer two thirds of the bovine vein wall (n=4), inflammatory foreign body reaction was most pronounced (FIGURE 13). Additionally, dystrophic mineralization of the prosthetic collagen, infiltration by macrophages, granulocytes, and a few lymphocytes were also seen. Microscopic examination of one of the bioprosthesis showed marked hemorrhage dissecting the collagen fibers of the bioprosthesis, purulent inflammation, and a few cocci.

Possibly, contamination at the time of bioprosthesis implantation could explain the presence of bacteria. In all animals (n=4), lymph nodes adjacent to the bioprostheses demonstrated marked histiocytosis.

Our histopathologic studies confirm the lack of thrombus formation within the vein leaflets, which appears intact, without fenestrations. A foreign body reaction was noted, particularly in the outer aspect of the graft. Viable endothelial cells were present within the leaflets. The implications of these observations are not clear, but may represent the early attempts to transform the graft tissue into host tissue. It may also suggest that the leaflets are relatively protected from immunogenic reaction, and therefore free of thrombus formation.

Our short-term animal experience suggests that, using a stent skeleton, it is possible to implant a glutaraldehyde-fixed bovine vein with leaflets into the swine central venous system, and to maintain valvular competence for at least two weeks. Thus, bovine vein is a reasonable preliminary choice for bioprosthesis construction, and this belief is supported by reports that glutaraldehyde fixation renders bovine vein valve biocompatible and non-thrombogenic. See, e.g., DeLaria GA, et al., "Hemodynamic evaluation of bioprosthetic venous prosthesis," *J Vasc Surg*, 1993,18:577-586; and Wang SK, et al. "In vitro performance of venous valve prostheses: an experimental model study, " *ASAIO Journal*, 1992:M213-M215.

Our study was preliminary in that it had several potential shortcomings. First, the experiments were conducted in an animal model with healthy veins. Second, the device was not tested in the upright position. Finally, the need for a better anticoagulation regimen is important based on our two anticoagulation-related complications. It is possible that a better vein apparatus for construction of the bioprosthesis may be an autologous glutaraldehyde-fixed or a cryopreserved vein

(Burkhart HM, et al., "Experimental repair of venous valvular insufficiency using cryopreserved venous valve allograft aided by a distal arteriovenous fistula," *J Vasc Surg*, 1997;26:817-822). In addition, several issues such as bioprosthesis durability, immunogenicity and leaflet function should be evaluated with long term studies. Nevertheless, our experience suggests that percutaneous placement of a venous bioprosthesis is technically feasible and, on a short-term basis, an effective means of restoring valve competence, particularly when the implanted vein segment has been trimmed to substantially reduce its wall thickness.

Moreover we recognize that a percutaneously implantable bioprosthesis has several potential advantages, including the minimally invasive nature of the procedure; it does not preclude the possibility of future re-intervention, either percutaneous, conservative treatments, or conventional surgical treatments; and it involves potentially lower costs.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims. Thus, for example, while we have described the preparation of a venous valve prosthesis using a vein segment obtained from a particular vessel in a particular biological source other than the host or patient, the invention is not to be limited thereto. Indeed, a different vessel could be the source of the vein segment, and the donor could be the patient. Moreover, while the invention has been described with reference to the implantation of a bioprosthesis in a vein, it is to be understood that a bioprosthesis of the type described herein could be implanted in an another biological duct to provide/restore valvular function therein.

WHAT IS CLAIMED IS:

1. A valve prosthesis, comprising:

a self-expanding, generally cylindrical stent component having first and second longitudinal ends and a hollow bore defined therethrough, said stent component being self-expandable from a first, reduced diameter for percutaneous deployment to a target portion of an animal vessel, to a second, expanded diameter to appose the wall of the vessel in said target portion; and

a segment of vein extracted from a biological source, the vein segment having an outer wall, a fluid flow passage defined therethrough, and a venous valve disposed therewithin for selectively precluding flow in one longitudinal direction through said passage, said vein segment having an outer wall thickness that is substantially reduced with respect to a thickness thereof upon extraction, by dissection of tissue from said outer wall;

said vein segment being co-axially disposed within said stent component and secured with respect thereto by at least one suture.

2. A valve prosthesis as in claim 1, wherein said vein segment outer wall is trimmed to a thickness that is at least about 50 percent reduced with respect to a pre-trimming thickness thereof.

3. A valve prosthesis as in claim 1, wherein in said vein segment has an axial length that is less than axial length of said stent component and said vein segment is disposed within said stent component so that each longitudinal end of said vein segment is axially spaced from a respective longitudinal end of said stent component, whereby said stent component and vein segment assembly define a stepped transition at each longitudinal end thereof.

4. A valve prosthesis as in claim 1, wherein said self-expanding stent component is formed from Nitinol.

5. A valve prosthesis as in claim 1, wherein said self-expanding stent component has a substantially continuous, mesh-like outer wall structure.

6. A valve prosthesis as in claim 1, wherein said vein segment has been preserved by exposing the same to a chemical fixing agent and wherein said vein segment is trimmed after it has been preserved.

7. A method of forming a valve prosthesis comprising:

providing a self-expanding, generally cylindrical stent component having first and second longitudinal ends and a hollow bore defined therethrough, said stent component being self-expandable from a first, reduced diameter for percutaneous deployment to a target portion of an animal vessel, to a second, expanded diameter to appose the wall of the vessel in said target portion;

providing a segment of vein that has been extracted from a biological source, the vein segment having an outer wall, a fluid flow passage defined therethrough, and a venous valve disposed therewithin for selectively precluding flow in one longitudinal direction through said passage;

trimming said vein segment by dissection of tissue from said outer wall thereof to substantially reduce a thickness of said outer wall with respect to a thickness thereof upon extraction from said biological source;

disposing said vein segment coaxially within said stent component; and

suturing said vein segment to said stent component

8. A method as in claim 7, wherein said suturing step comprises suturing said vein segment to said stent component with at least one running suture extending at least about a substantial portion of a length of said vein segment.

9. A method as in claim 7, wherein said the trimming step comprises trimming said vein segment outer wall to a thickness that is at least about 50 percent reduced with respect to a pre-trimming thickness thereof.

10. A method as in claim 7, wherein said the trimming step further comprises trimming an axial length of said vein segment so that a length of said vein segment is not greater than a length of said stent component.

11. A method as in claim 10, wherein said axial length of the vein segment is less than a length of said stent component and said vein segment is disposed within said stent component so that each longitudinal end of said vein segment is axially spaced from a respective longitudinal end of said stent component, whereby an assembly of said stent component and vein segment define a stepped transition at each longitudinal end thereof.

12. A method as in claim 7, wherein said step of providing a stent component comprises providing a self-expanding stent component formed from Nitinol.

13. A method as in claim 7, wherein said step of providing a stent component comprises providing a self-expanding stent component has a substantially continuous, mesh-like outer wall structure.

14. A method as in claim 7, wherein said step of providing a segment of vein comprises providing a vein segment that has been preserved by exposing the same to a chemical fixing agent and wherein said vein segment is trimmed after it has been preserved.

15. A method of providing a valve function within a tubular duct of a patient comprising the steps of:

extracting a vein segment from a biological source, the vein segment having an outer wall, a fluid flow passage defined therethrough, and a venous valve disposed therewithin for selectively precluding flow in one longitudinal direction through said passage;

preserving the venous valve so that the valve within said vein segment is competent under venous conditions;

trimming the preserved vein segment to substantially reduce a thickness of said outer wall thereof;

providing a self-expanding, generally cylindrical stent component having first and second longitudinal ends and a hollow bore defined therethrough, said stent component being self-expandable from a first, reduced diameter for percutaneous deployment to a target portion of the tubular duct of the patient, to a second, expanded diameter to appose the wall of the duct in said target portion;

disposing the trimmed vein segment within the interior of the stent component;

securing vein segment to the stent component to define a bioprosthesis;

reducing an outer diameter of said bioprosthesis to said first, reduced diameter;

percutaneously transporting said bioprosthesis to a target portion of the tubular duct of the patient; and

allowing said bioprosthesis to self-expand to said second, expanded diameter.

16. A method as in claim 15, wherein said the trimming step comprises trimming said vein segment outer wall to a thickness that is at least about 50 percent reduced with respect to a pre-trimming thickness thereof.

17. A method as in claim 15, wherein said step of preserving comprises exposing the vein segment to a chemical fixing agent.

18. A method as in claim 17, wherein fixing agent is glutaraldehyde.

19. A method as in claim 15, wherein said stent structure is formed from Nitinol and said step of reducing an outer diameter of said bioprosthesis comprises cooling the bioprosthesis to reduce an outer diameter thereof.

20. A method as in claim 19, wherein said step of percutaneously transporting comprises percutaneously guiding a deployment sheath over a guidewire through the tubular duct of the patient so that a distal end thereof is disposed adjacent said target portion of said duct; removing said guide wire; loading said reduced diameter bioprosthesis into said deployment sheath; displacing said bioprosthesis along said deployment sheath to said distal end portion of said deployment sheath; withdrawing said deployment sheath with respect to said bioprosthesis; whereby said bioprosthesis is disposed in said target portion of said duct; and allowing said bioprosthesis to self expand.

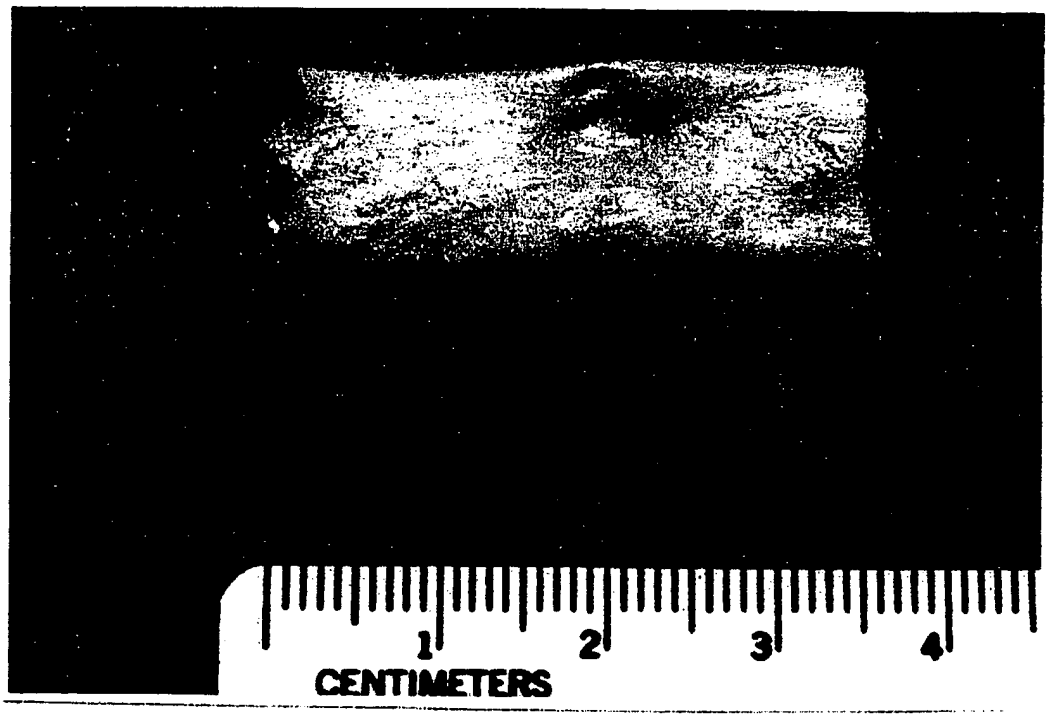

Fig. 1

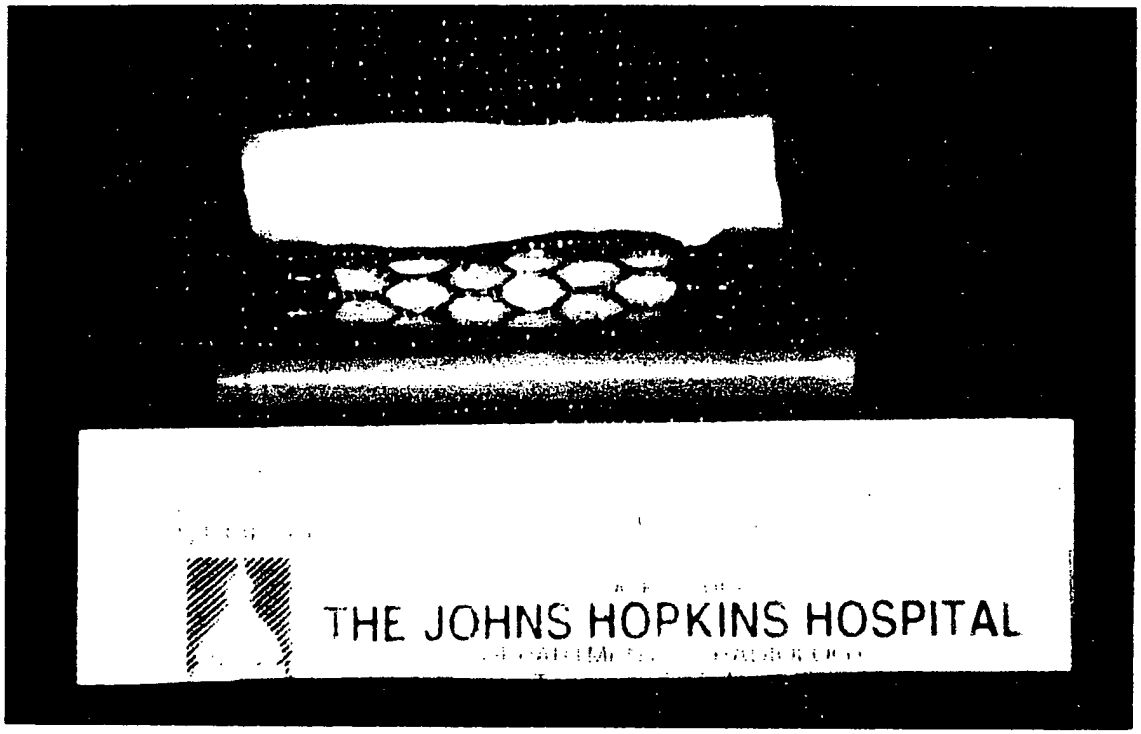

Fig. 2

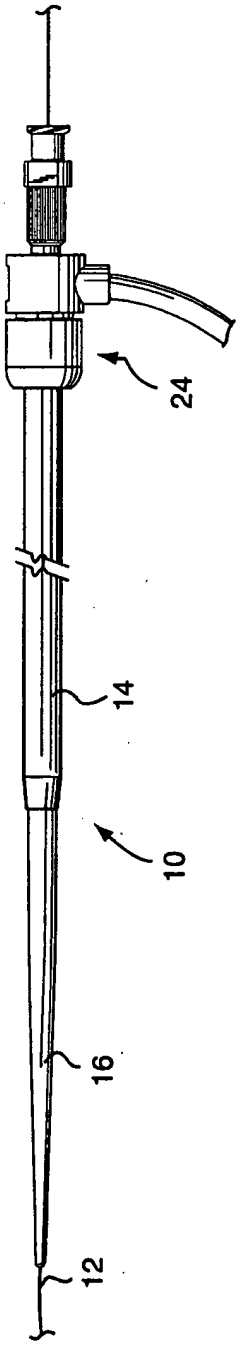

Fig. 3

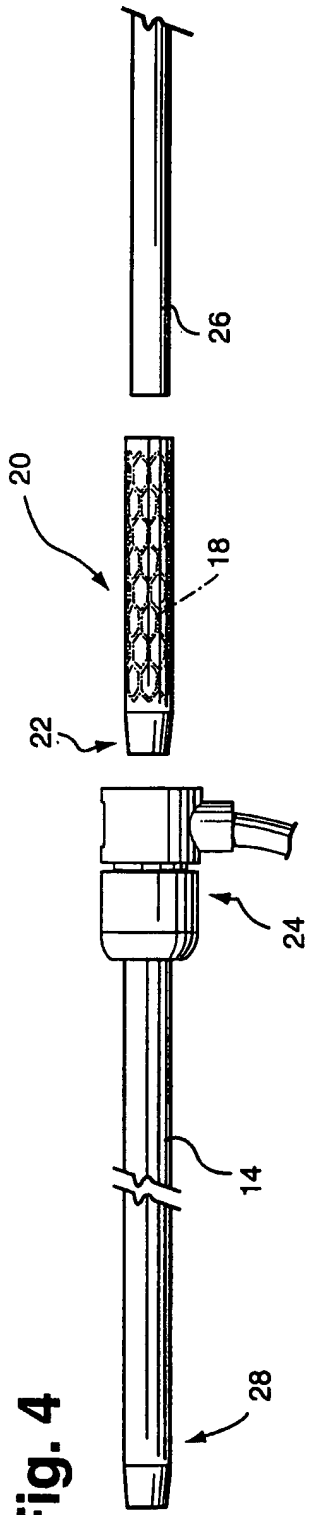

Fig. 4

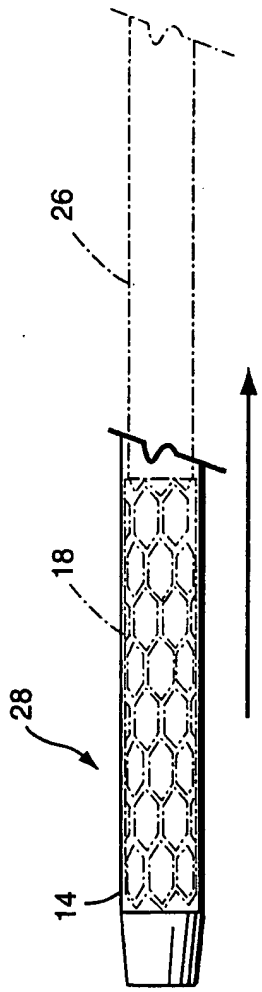

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

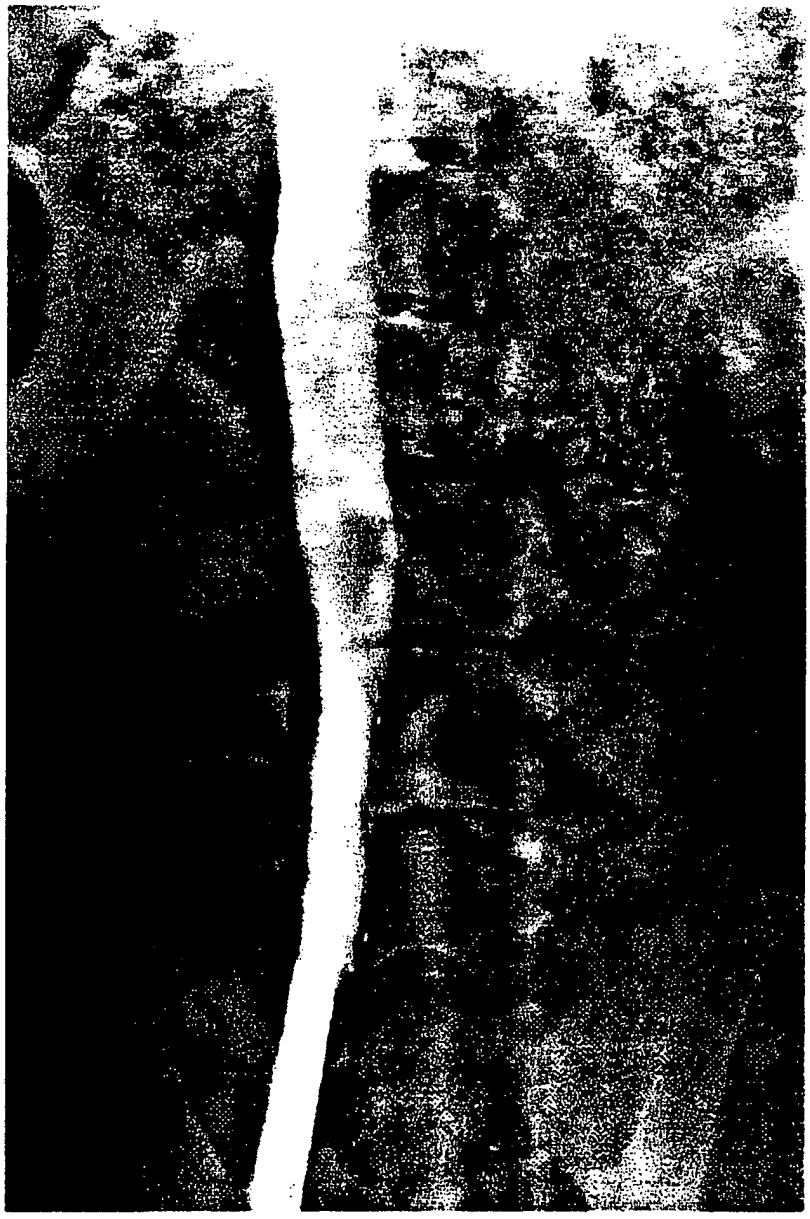

Fig. 10

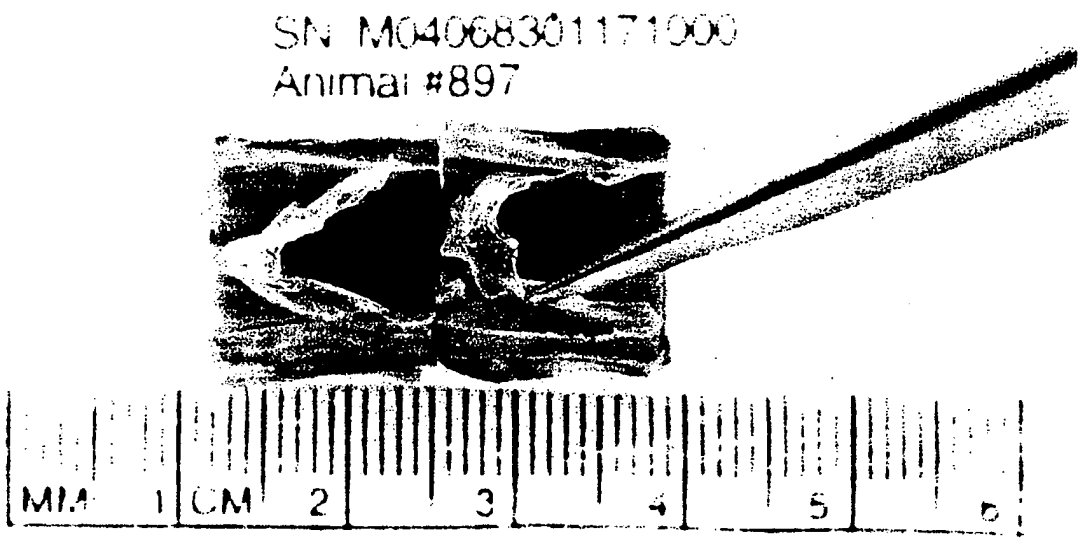

Fig. 11

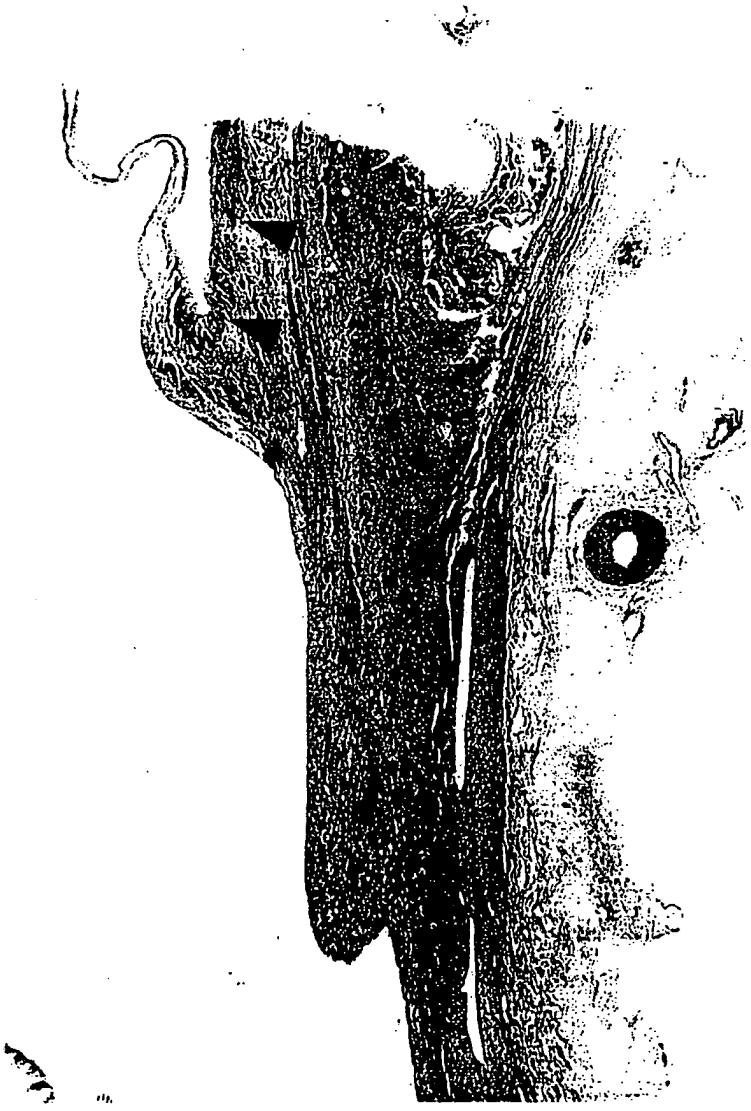

Fig. 12

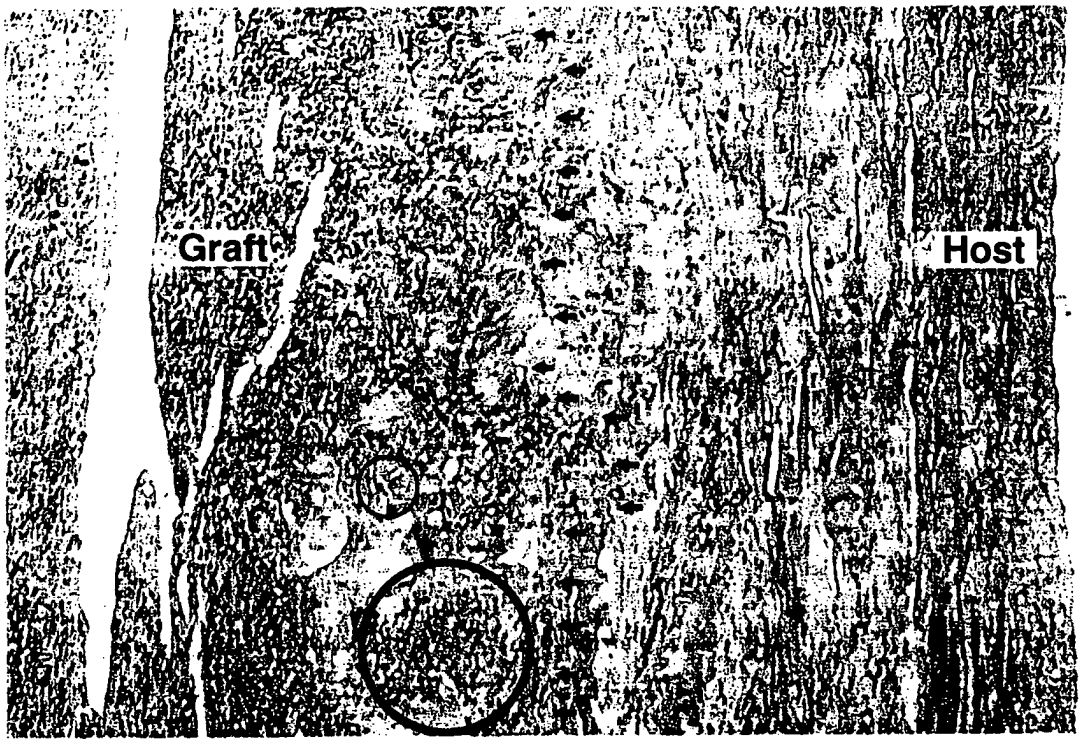

Fig. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03603

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61F 2/06
US CL :623/1.13, 1.2, 1.24
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/153-156; 623/1.13, 1.2, 1.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST
Search Terms: vein, stent, biological, tissue, preserved, graft, prosthesis, implant, natural, self-expanding, Nitinol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,131,908 A (DARDIK et al.) 21 July 1992, col. 8 lines 56-66.	1-20
Y	US 5,609,626 A (QUIJANO et al.) 11 March 1997, col. 5 line 36 to col. 6 line 38.	1-20
Y	US 5,800,522 A (CAMPBELL et al.) 01 September 1998, col. 7 lines 16-31.	1-20
A	US 5,855,601 A (BESSLER et al.) 05 January 1999, entire document.	1-20
A	US 5,865,723 A (LOVE) 02 February 1999, col. 4 line 66 to col. 5 line 65.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 JUNE 2000	29 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TRAM A. NGUYEN Telephone No. (703) 308-0804

Form PCT/ISA/210 (second sheet) (July 1998)*